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Sexual differentiation of the brain and behavior

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During the intrauterine period the human brain develops in the male direction via direct action of a boy's testosterone, and in the female direction through the absence of this hormone in a girl. During this time, gender identity (the feeling of being a man or a woman), sexual orientation, and other behaviors are programmed. As sexual differentiation of the genitals takes places in the first 2 months of pregnancy, and sexual differentiation of the brain starts during the second half of pregnancy, these two processes may be influenced independently of each other, resulting in transsexuality. This also means that in the case of an ambiguous gender at birth, the degree of masculinization of the genitals may not reflect the same degree of masculinization of the brain. Differences in brain structures and brain functions have been found that are related to sexual orientation and gender.

Key words: gender identity; sexual orientation; sexual differentiation of the human brain; transsexuality; homosexuality; intrauterine development.

ORGANIZATION AND ACTIVATION OF THE HUMAN BRAIN

Sexual differentiation of the brain brings about permanent changes in brain structures and functions via interaction of the developing neurons with the environment in its widest sense. The environment of a neuron is formed by the surrounding nerve cells and the child's circulating hormones, as well as the hormones, nutrients, medication and other chemical substances from the environment that enter the fetal circulation via the mother. All these factors may have a lasting effect on the process of sexual differentiation of the brain.

The testicles and ovaries develop in the sixth week of pregnancy. This happens under the influence of a cascade of genes, such as the sex-determining gene on the Y chromosome (the SRY), in which many factors play a role. The production of the

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androgens testosterone and dihydrotestosterone by a boy's testes is necessary for the sexual differentiation of the sexual organs between weeks 6 and 12 of pregnancy. The peripheral conversion of testosterone into dihydrotestosterone is essential for the formation of a boy's penis, prostate and scrotum. The development of the female sexual organs in the womb is primarily based on the absence of androgens.[1]

Once the differentiation of the sexual organs into male or female is settled, determined by the presence or absence of the Y chromosome of the father, the next thing to differentiate is the brain, in particular due to the influence of sex hormones on the developing brain cells. This involves (permanent) organizational changes, while during puberty the brain circuits that developed in the womb are activated by sex hormones.

A girl's brain is protected against the effect of circulating estrogens from the mother by the protein α-fetoprotein, which is produced by the fetus and binds strongly to estrogens but not to testosterone.[2] However, the brain itself is also capable of producing estrogens. Testosterone may thus not only have a direct effect on a boy's brain, but, once converted into estrogens by aromatase, it may also act on developing neurons. In rats, this conversion is the most important mechanism for the virilization of the brain[3], but this is not the case in human gender identity and sexual orientation (see below). The fact that there are probably direct genetic effects that affect the sexual differentiation of the brain without involving the sex-hormone receptors is a further complication. Some fetal rat brain cells undergo sexual differentiation, even in tissue culture, without the involvement of sex hormones. Moreover, in adult men the genes SRY and ZRY are expressed until very advanced ages, even though strictly speaking these genes stopped playing a role in sexual differentiation some 80 years earlier.[4] There are at present many additional candidate genes for a role in sexual differentiation of the brain without the involvement of hormones, since it has been found in mouse fetus that, even before the hormones come into play, 50 genes are expressed at different levels in the brains of male and female fetuses.[5] Also genes that escape inactivation on the X chromosome could contribute to the sexually dimorphic expression levels of genes, and thus to sexual dimorphic functions.[6] Thus the sexual differentiation of the brain is not only caused by hormones, even though they are very important for gender identity and sexual orientation.

SEX HORMONES AND BRAIN DEVELOPMENT

During fetal development, the brain is influenced by sex hormones such as testosterone, estrogens and progesterone. From the earliest stages of fetal brain development onwards, many neurons throughout the entire nervous system already have receptors for these hormones. The early development of boys shows two periods during which the testosterone levels are high. The first peak occurs during mid-pregnancy. Testosterone levels peak in the fetal serum between weeks 12 and 18 of pregnancy.[7] In weeks 34–41 of pregnancy the testosterone levels of boys are 10 times higher than those of girls.[8]

The second peak takes place in the first 3 months after birth. At the end of the pregnancy, when α-fetoprotein declines, the fetus is more exposed to estrogens from the placenta, which inhibits the hypothalamus–hypophysial–gonadal axis of the child. This inhibition is lost once the child is born, which causes a peak in testosterone in boys and a peak in estrogens in girls.[9] The testosterone level in boys at this time is as high as it will be in adulthood, although a large part of it circulates bound. Also at this time the testosterone level is a factor higher in boys than in girls. During these two periods there are thus no high levels of testosterone in girls. These two peaks

of testosterone are said to fix the development of structures and circuits in the brain for the rest of a person's life (= programming or organizing). The rising hormone levels during puberty 'activate' circuits that were built during development, and behavioral patterns and disorders that originated much earlier in development, such as schizophrenia, are expressed.[1]

The different brain structures that result from the interaction between hormones and developing brain cells are thought to be the basis of sex differences in the structure of the brain, and thus for behavior, gender identity (the feeling of being either a man or a woman), gender role (behaving as a man or a woman in society), sexual orientation (heterosexuality, homosexuality or transsexuality) and sex differences regarding cognition and aggressive behavior. Factors that interfere with the interaction between hormones and the developing brain systems during development in the womb may permanently influence later behavior. As the sexual differentiation of the genitals takes places much earlier on in development (in the first 2 months of pregnancy) than the sexual differentiation of the brain (starting in the second semester of pregnancy and becoming overt upon reaching adulthood), these two processes may be influenced independently of each other, which may result in people with male sexual organs who feel female and vice versa (a phenomenon called transsexuality). However, this also means that in the case of an ambiguous sex at birth, the degree of masculinization of the genitals may not reflect the same degree of masculinization of the brain.[1]

SEX DIFFERENCES IN COGNITION AND AGGRESSION: LITTLE EFFECT OF THE SOCIAL ENVIRONMENT

In the 1960s and 1970s it was postulated that a child was born as a tabula rasa and that it was forced into the male or female direction by society's conventions. J. Money put this as follows: '*Gender identity is sufficiently incompletely differentiated at birth as to permit successful assignment of a genetic male as a girl. Gender identity then differentiates in keeping with the experiences of rearing.*'[10] This concept has had devastating results (see later: the John–Joan–John case).[11]

One of the stereotypical behavioral differences between boys and girls, which it has often been said are forced upon them by upbringing and social environment, is their behavior in play. Boys are more active and wilder, and they prefer to play with cars, whereas girls prefer dolls. The idea that it is not society that forces these choices upon children but a sexual difference in the early development of their brains and behavior was supported by a study by Alexander and Hines[12], who offered dolls, toy cars and balls to green vervet monkeys. The female monkeys consistently chose the dolls and examined these ano-genitally, whereas the male monkeys were more interested in playing with the toy cars and with the ball. 'Neutral' toys, such as a picture book and a toy dog, did not show sex differences in either humans or monkeys. Girls who are exposed to too much testosterone in the womb, in the case of congenital adrenal hyperplasia (CAH), tend to choose boys as playmates, play preferentially with boys' toys, and are generally wilder than other girls, and are called tomboys.[13] It thus seems as if the sexual differences in play behavior originated early on in our evolution, before the hominids, and that they are imprinted during intrauterine development under the influence of sex hormones.

A similar conclusion can be drawn with respect to sex differences in spontaneous drawings. Japanese research shows that subject matter, choice of color and composition

of drawings by boys and girls show clear sex differences, influenced by the hormones to which the child's brain was exposed in the womb. Girls tend to draw human figures, mainly girls and women, flowers and butterflies. They use bright colors, such as red, orange and yellow. Their subjects tend to be peaceful and arranged in a row on the ground. Boys, however, prefer to draw more technical objects, weapons and fighting, and means of transport, such as cars, trains and airplanes, in birds-eye view compositions and in dark, cool colors such as blue. Drawings by girls exposed to too high testosterone levels in the womb due to CAH begin to show male characteristics some 5–6 years later, even when treated immediately after birth.[14] Also, girls with CAH have a bigger chance of being lesbian or transsexual. Apparently exposure to higher levels of male hormones has important and lasting effects on behavior, and the sex differences that are revealed through drawings are determined by the hormones in the womb rather than by what society demands later on.

The well-known story of John–Joan–John (a pseudonym of David Reimer)[11] means that the concept of sexual neutrality at birth, as introduced by John Money in the 1950s, is suspect. According to Money, gender imprinting does not start until the age of 1 year, and its development will be far advanced by the age of 3–4 years.[15] This was the basis for the decision to make a girl out of an 8-month-old boy who lost his penis due to a mistake during minor surgery (i.e. a phimosis operation). The testicles of this child were removed before the age of 17 months in order to facilitate feminization. The child was dressed in girl's clothes, received psychological counseling and was given estrogens in puberty. Money described the development of this child as a normal female. However, later on Milton Diamond made it clear that this had not at all been the case. In adulthood the child changed back to male, married, and adopted a few children.[16] Unfortunately, he lost money on the stock exchange, got divorced, and eventually committed suicide in May 2004. This story illustrates the enormous programming influence of the intrauterine period on gender.

The apparent impossibility of getting someone to change their sexual orientation is a major argument against the importance of the social environment in the emergence of homosexuality, as well as against the idea that homosexuality is a lifestyle choice. The mind boggles at what has been attempted in order to achieve this: hormonal treatments such as castration, administration of testosterone or estrogens (treatments that appeared to affect libido but not sexual orientation); psychoanalysis; apomorfine serving as an emetic in combination with homo-erotic pictures; psychosurgery (lesions in the hypothalamus); electroshock treatment; chemical induction of epileptic insults; and imprisonment. As none of these interventions has led to a well-documented change in sexual orientation[17], there can be little doubt that sexual orientation has become fixed in adulthood and is beyond influencing later. Changes in sexual orientation in adulthood have been described – e.g. from heterosexual to pedophile – but only in cases of brain tumors in the hypothalamus and prefrontal cortex.[18,19] However, such devastating changes in the hypothalamus cannot be interpreted in terms of functional changes in particular neuronal circuits. There are also claims of a change from pedophiles and homosexual men into heterosexual behavior through stereotactical psychosurgery by means of lesions in the nucleus ventromedialis[20], but these interventions are not only of questionable ethical quality, they also do not meet any scientific standard and thus cannot teach us anything. There are also some recent publications postulating that the sexual orientation of homosexual women, more than that of homosexual men, may sometimes change, either spontaneously or under the influence of psychotherapy.[21] The effectiveness of therapy and the absence of bisexuality has, however, never been convincingly shown in these cases.

THE MECHANISM OF SEXUAL DIFFERENTIATION OF THE BRAIN: NEUROBIOLOGICAL FACTORS

In male rats, testosterone is turned into estrogens locally in the brain, and these estrogens then masculinize the brain. In humans, however, the main mechanism appears to involve the *direct* effects of testosterone on the developing brain. The androgen insensitivity syndrome is caused by mutations in the receptor gene for androgens. Despite their genetic (XY) masculinity, these individuals develop as phenotypical women and experience their sexual orientation, fantasies and experiences as 'heterosexual', without gender problems.[22]

On the other hand, when a boy has a 5α-reductase-2 or 17β-hydroxy-steroid dehydrogenase-3 deficiency preventing peripheral testosterone from being transformed into dihydrotestosterone, a 'girl' with a large clitoris is born. These children are generally raised as girls. However, when the testosterone production goes up in these XY children during puberty, this 'clitoris' grows to penis size, the testicles descend, and the child's build begins to masculinize and become muscular. Despite the fact that these children are raised as girls, the majority (60%) change into heterosexual males[23–26], apparently due to the organizing effect of testosterone on early brain development.

Boys who are born with a cloacal exstrophy – i.e. with bladder exstrophy and a partly or wholly absent penis – are usually changed into girls immediately after birth. A recent survey shows that in adulthood only 65% of these children who were changed into girls continue to live as girls, and when individuals with gender dysphoria are excluded this number is 47%.[27,28] From these examples it appears that the direct action of testosterone on the developing brain in boys is of the utmost importance for the development of the male gender and heterosexual orientation. Moreover, studies on cloacal exstrophy suggest that the postnatal testosterone peak is not crucial for gender development, because these children generally undergo operation shortly after birth.

TRANSSEXUALITY

Transsexuality is characterized by a conviction of having been born in the wrong body. The prevalence of transsexuality is 1:10,000 for male-to-female transsexuals and 1:30,000 for female-to-male transsexuals. Gender problems often crop up even early in development. Mothers report that, from the moment their sons learned to talk, they insisted on wearing their mother's clothes and shoes, only showed an interest in girls' toys, and mostly played with girls. On the other hand, not all children with gender issues eventually become transsexual. Only in 23% of the cases does a childhood gender problem lead to transsexuality in adulthood.[29,30]

There is a vast array of factors that may lead to gender problems (Table 1). Twin and family research has shown that genetic factors play a part.[30] Rare chromosomal abnormalities may lead to transsexuality, and it was recently found that polymorphisms of the genes for the estrogen receptors α and β and for aromatase also produced an increased risk.[31] Abnormal hormone levels during early development may play a role, as suggested by the high frequency of polycystic ovaries, oligomenorrhea and amenorrhea in female-to-male transsexuals. This observation points to an early intrauterine exposure of the female fetus to abnormally high levels of testosterone.[32] The chance of a girl becoming transsexual in the case of congenital adrenal hyperplasia (CAH),

Table 1. Prenatal factors that influence gender identity (the feeling of being a man or a woman) and that may result in transsexuality.

Genetic factors	Rare chromosomal disorders[1]
	Twin studies[30]
	Polymorphisms in estrogen-receptor-β, androgen receptor and aromatase genes[31]
Phenobarbital/diphantoin	taken by pregnant mother[35]
Hormones	Cloacal extrophy[27,28]
	5 α-reductase-2 or 17β-hydroxy-steroid-dehydrogenase-3 deficiency[23,25,26]
	CAH girls[33,34,42]
	Complete androgen insensitivity syndrome results in XY heterosexual females[22]
	DES sons: 25% gender problems[36]
Social factors?	Postnatally no evidence[1,11,16,29]

when she has been exposed to extreme levels of testosterone in utero, is also greater. Although the chances of transsexuality in these cases are a factor of 300–1000 higher than normal, the risk for transsexuality in this condition is still only 1–3%[33], whereas the chances of serious gender problems are 5.2%.[34] The consensus is, therefore, that girls with CAH should be raised as girls, even when they are masculinized.[24]

Epileptic women who were given phenobarbital or diphantoin during pregnancy also have an increased risk of giving birth to a transsexual child. Both these substances change the metabolism of the sex hormones and can act on the sexual differentiation of the brains of the child. In a group of 243 women who had been exposed to such substances during pregnancy, Dessens et al[35] found three transsexual children and a few more with less radical gender problems; these are relatively large numbers for such a rare condition. On their website these 'DES' (diethylstilbestrol, an estrogen-like substance – see later) sons claim a transsexuality percentage of 35.5% and a gender problem percentage of 14.3%.[36] This is alarming, but needs, of course, to be confirmed in a formal study.

There are no indications that postnatal social factors could be responsible for the occurrence of transsexuality.[29]

Transsexuality and the brain

The theory of the origin of transsexuality is based on the fact that the differentiation of sexual organs takes place during the first couple of months of pregnancy, before the sexual differentiation of the brain. As these two processes have different timetables, it is possible, in principle, that they take different routes under the influence of the factors. If that is the case, one would expect, in transsexuals, female structures in a male brain and vice versa, and indeed, we did find such a reversal in the central nucleus of the bed nucleus of the stria terminalis (BSTc), a brain structure that, in rats, is involved in many aspects of sexual behavior (Figures 1 and 2). However, a gender identity test for a rat does not exist, and this can therefore be studied only in humans.

We did indeed find a clear sex difference in the human BSTc. In men this area is twice the size of that in women and contains twice as many somatostatin neurons. No difference was found regarding size or number of neurons in this area in relation

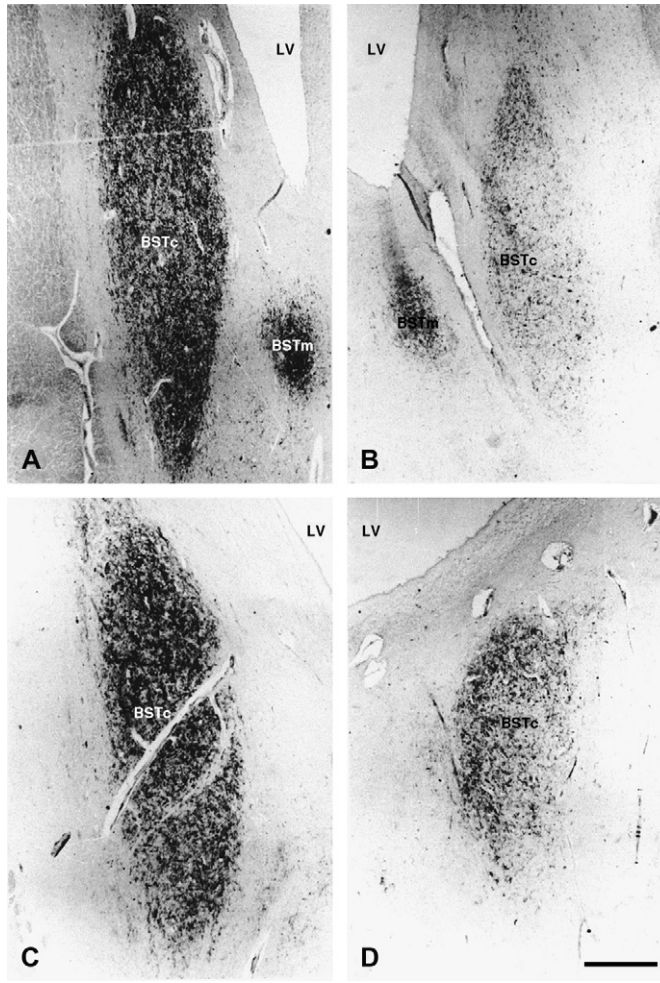

Figure 1. Representative slides of the central part of the bed nucleus of the stria terminalis (BSTc) innervated by fibers stained for vasoactive intestinal polypeptide (VIP). BSTm is the small medial part of the BST. (A) Heterosexual man. (B) Heterosexual woman. (C) Homosexual man. (D) Male-to-female transsexual. Scale bar 0.5 mm. LV, lateral ventricle. Note the sex difference (A versus B), and that the male-to-female transsexual (D) has a female BSTc as far as size and innervation are concerned. From Zhou et al (1995, *Nature* **378:** 68–70) with permission.

to sexual orientation. In male-to-female transsexuals we found a completely female BSTc. Until now we have only been able to obtain material from one female-to-male transsexual, and his BSTc indeed turned out to have all the male characteristics. We were able to exclude the possibility that the reversal of sex differences in the BSTc were caused by changing hormone levels in adulthood[37,38], and it therefore seems that we are dealing with a developmental effect. Our observations thus support the above-mentioned neurobiological theory about the origin of transsexuality. The size of the BSTc and the number of neurons match the gender that transsexuals feel they belong to, and not the sex of their sexual organs, birth certificate or

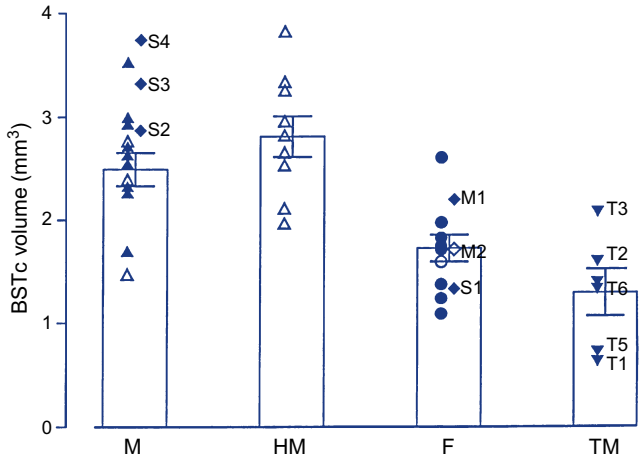

Figure 2. Volume of the bed nucleus of the stria terminalis (BSTc) innervated by fibers stained for vasoactive intestinal polypeptide (VIP) in heterosexual men (M), homosexual men (HM), heterosexual women (F) and male-to-female transsexuals (TM; T1–T6). Patients with abnormal sex-hormone levels are numbered S1–S4. M1 and M2, postmenopausal women. The distribution is mean ± SEM. Open symbols: individuals who died of AIDS. Note the sex difference regarding the volume of the BSTc, the fact that the volume is not affected by abnormal hormone levels in adulthood, and that the volume of the male-to-female transsexuals is female. From Zhou et al (1995, *Nature* **378:** 68–70) with permission.

passport. Unfortunately, the sex difference in the BSTc does not become apparent in the BSTc volume until early adulthood[39], and this neuroanatomical sex difference therefore cannot play a part in the early diagnosis of transsexuality.

SEXUAL ORIENTATION: HETEROSEXUALITY, HOMOSEXUALITY AND BISEXUALITY

Sexual orientation in humans is also determined during early development, under the influence of our genetic background and factors that influence the interactions between the sex hormones and the developing brain (see Table 2).

The importance of genetic factors has become apparent from twin and family research. According to LeVay and Hamer[40], the size of the genetic component in homosexuality for both sexes is over 50%. Which genes play a role here is not yet clear. It is interesting that such a genetic factor has held its own in the population through evolution, as homosexuals do not tend to procreate as much as other members of the group. A good explanation could be that the genetic factors that are responsible for homosexuality also have a beneficial effect on the procreation of the group as a whole. Indeed, Camperio-Ciani et al[41] have found that women on a homosexual male's mother's side tend to be more fertile.

Abnormal hormone levels from the child itself during intrauterine development may influence sexual orientation, as is apparent from the large percentage of bisexual and homosexual girls with CAH.[33,42] Between 1939 and 1960 some 2 million pregnant women in the US and Europe were prescribed diethylstilbestrol (DES) in order to prevent miscarriage. DES turned out not to prevent miscarriage. It is an estrogen-like substance that, in small dosages, does not only give a slightly elevated risk of cervical

Table 2. Prenatal factors that may influence sexual orientation (homosexuality, heterosexuality, bisexuality).

Genetic factors	Twin studies[62,40] Molecular genetics[1]
Hormones	CAH girls[1,33,42] DES[1,43]
Chemicals	Prenatal exposure to nicotine, amphetamine, or thyroid medication[48,49]
Immune response	Homosexual orientation in men is most likely to occur in men with a large number of older brothers[46,47]
Social factors?	Stress of the mother during pregnancy[48,50,51] Being raised by transsexual or homosexual parents does not affect sexual orientation[52]

cancer but also increases the chance of bisexuality or homosexuality in girls[43,44] (but see Titus-Ernstoff et al).[45]

The chance that a boy will be homosexual increases with the number of older brothers. This phenomenon is explained by an immunological response by the mother to a product of the Y chromosome of the sons; the chance of such a response to male factors would increase with every pregnancy resulting in the birth of a son.[46,47]

Prenatal exposure to nicotine, amphetamine, or thyroid-gland hormones increases the chances of giving birth to lesbian daughters.[48,49] A stressed pregnant woman has a bigger chance of giving birth to a homosexual son[48,50] or a lesbian daughter.[51]

Although it has often been postulated that postnatal development is also important for the direction of differentiation, there is no solid proof for this. On the contrary, children who were born after artificial insemination with donor sperm and who were raised by a lesbian couple are heterosexually oriented.[52] There is also no proof for the idea that homosexuality is the result of a deficient upbringing, or that it is a 'life-style choice' or would be brought about by social learning.[17] It is curious, therefore, that some children are still forbidden to play with homosexual friends, an unimaginable relic from the idea that homosexuality would be contagious.

SEXUAL ORIENTATION AND THE BRAIN

Clinical observations have shown the involvement of a number of brain structures in sexual orientation. It has been reported that in some patients with the Klüver–Bucy syndrome, which involves lesions of the temporal lobe, orientation changed from heterosexual to homosexual. Shifts in sexual orientation (to homosexual and pedophile) have also been reported in connection with tumors in the temporal lobe and hypothalamus. Lesions in the preoptic area of the hypothalamus in experimental animals such as ferrets and rats also show shifts in sexual orientation.[1,53]

Several structural and functional differences in the brain have been described in relation to sexual orientation (Figure 3). We found the first difference in the suprachiasmatic nucleus (SCN), the clock of the brain, which in homosexual men turned out to be twice the size of that in heterosexual men.[54] In an experiment with rats a similar difference could be induced by pharmacologically disturbing the interaction between testosterone and the developing brain around the time of birth. This experiment yielded bisexual adult rats which had larger numbers of cells in their SCN.[55] The difference in

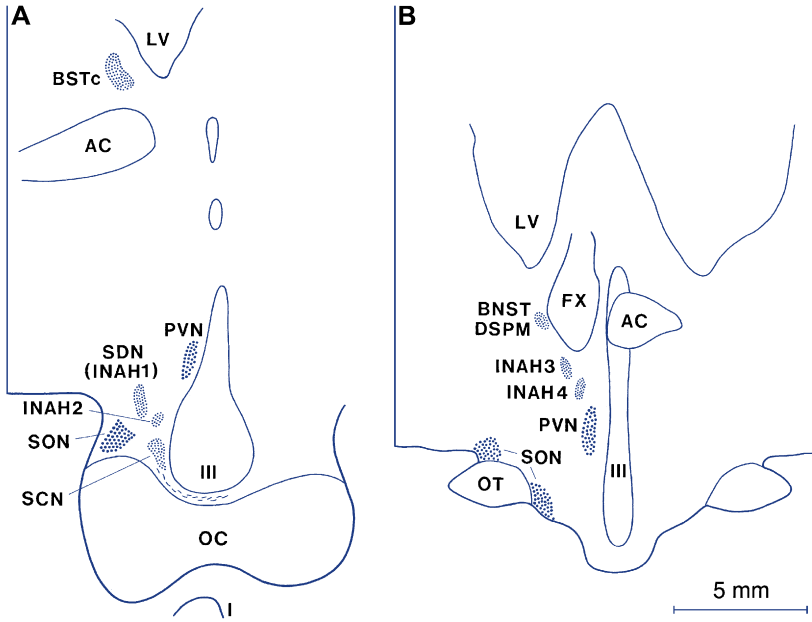

Figure 3. Scheme of the sexually dimorphic structures in the hypothalamus of man. (A) is more rostral than (B). III, third ventricle; AC, anterior commissure; BNST-DSPM, darkly staining posteromedial component of the bed nucleus of the stria terminalis; FX, fornix; I, infundibulum; INAH1–4, interstitial nucleus of the anterior hypothalamus 1–4; LV, lateral ventricle; OC, optic chiasm; OT, optic tract; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus; SDN, sexually dimorphic nucleus of the preoptic area (= INAH-1); SON, supraoptic nucleus. Scale bar = 5 mm. The AC, BSTc, BNST-DSPM, INAH2, 3, 4, SCN and SDN are different in men and women. The SCN and INAH-3 differ according to sexual orientation. From Swaab (2003, in *Handbook of Clinical Neurology* Aminoff MJ et al (series eds). Amsterdam, Elsevier: 476 pp) with permission.

the SCN was therefore not caused by a change in sexual behavior, as is sometimes suggested, but by a disturbed interaction between sex hormones and the developing brain.

In 1991, LeVay[56] reported that homosexual men, just like heterosexual women, have a smaller area in the frontal part of the hypothalamus (INAH-3). In 1992, Allen and Gorski[57] reported that the anterior commissure of homosexual men is larger than that of heterosexual men. This structure, which is larger in women than in men, takes care of left–right connections of the temporal cortex, and in this way is involved in sex differences related to cognitive abilities and language.

Functional scanning has recently also pointed out differences in the hypothalamus in relation to sexual orientation. The activity of the hypothalamus of homosexual men turned out not to be as responsive to a classic antidepressant (fluoxetine) as that of heterosexual men, which points to a different kind of activity of the serotonergic system.[58] Savic et al[59] made use of scent, a pheromone derived from progesterone and excreted in perspiration in concentrations that are 10 times higher in men than in women. Pheromones influence sexual behavior and stimulate activation in the hypothalamus of heterosexual women and homosexual men in the same way, but did not elicit a response in the hypothalamus of heterosexual men. Apparently heterosexual men are not stimulated by such a male scent, and pheromones thus seem to play a part in sexual behavior according to sexual orientation.

A follow-up study[60] showed that – in contrast to what happened in the frontal part of the hypothalamus in heterosexual women, where this pheromone elicited an activation – in lesbian women this substance was processed by the olfactory system and not by the frontal part of the hypothalamus. Moreover, when lesbian women were exposed to a pheromone derived from estrogens and excreted in the urine of pregnant women, they responded with an activation of the frontal part of the hypothalamus in a way that partly matched the pattern seen in heterosexual men. These observations, too, show that there are hypothalamic circuits that function in a way that depends on sexual orientation. Another study expands this conclusion to cortical areas. With functional magnetic resonance imaging (fMRI) the activity changes in the brain were measured while pictures of men and women were shown. Showing a female face made the thalamus and medial prefrontal cortex of heterosexual men and homosexual women react more strongly, whereas these structures reacted more strongly to the face of a man in homosexual men and heterosexual women.[61]

Neurobiological research in relation to sexual orientation in humans is only just beginning, but already it seems that we have a vast array of brain differences, not only in relation to gender, but also in relation to sexual orientation.

Practice points

- the human fetal brain develops in the male direction through direct action of a boy's testosterone and in the female direction through the absence of this hormone in a girl
- during the intrauterine period, gender identity (the feeling of being a man or a woman), sexual orientation, cognition, aggression and other behaviors are programmed in the brain in a sexually differentiated way
- as sexual differentiation of the genitals takes places in the first 2 months of pregnancy and sexual differentiation of the brain starts in the second half of pregnancy, this means that in the case of an ambiguous sex at birth, the degree of masculinization of the genitals may not reflect the same degree of masculinization of the brain
- our observations on a reversed sex difference in the brain support the idea that transsexuality is based on an opposite sexual differentiation of the brain in the second half of pregnancy and sexual differentiation of sexual organs during the first couple of months of pregnancy
- there is no proof that social environment after birth has an effect on the development of gender or sexual orientation

Research agenda

- the effects on sexual differentiation in the brain of endocrine disrupters in the environment and medicines given to the pregnant mother should be investigated
- structural and functional sex differences in the brain and their functional consequences for human health and disease should be subjected to a systematic and multidisciplinary study

SUMMARY

During the intrauterine period the brain develops in a male direction through direct action of a boy's testosterone on the developing nerve cells, and in a female direction through the absence of this hormone in a girl. In this way gender identity (the feeling of being a man or a woman) and our sexual orientation are programmed into our brain structures when we are still in the womb.

As the sexual differentiation of the genitals takes places much earlier in development (in the first 2 months of pregnancy) than the sexual differentiation of the brain (starting in the second half of pregnancy and becoming overt up until adulthood), these two processes may be influenced independently of each other, which may result in people with male sexual organs who feel female and vice versa (a phenomenon called transsexuality). However, this also means that in the case of an ambiguous sex at birth, the degree of masculinization of the genitals may not reflect the same degree of masculinization of the brain.

Sex differences are not only found in relation to gender and sexual orientation, but also in cognition, aggression, and many other behaviors.

Gender and sexual orientation are influenced by many biological factors (see Tables 1 and 2). There is no proof that social environment after birth has an effect on the development of gender or sexual orientation.

Differences in brain structures and brain functions have been found that are related to sexual orientation and gender.

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